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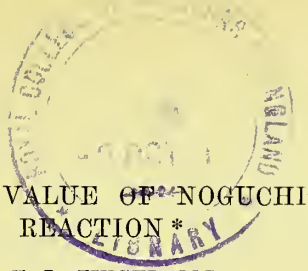
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THE PRACTICAL VALUE OF NOGUCHI'S LUETIN REACTION*

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The theoretical conception on which the luetin test is based is one which many investigators must have had in mind before Noguchi made its realization possible by discovering a means of growing the *Treponema pallidum* in pure culture. For instance, in an article on "Allergy," von Pirquet had prophesied:

> I personally feel quite sure that it will be possible to make the diagnosis of syphilis by cutaneous and subcutaneous inoculation as soon as the syphilis virus can be obtained in pure cultures.[1]

In the hope of obtaining a characteristic cutaneous reaction in syphilis various investigators abroad, as well as Schoenberg[2] of New York, inoculated or applied extracts of syphilitic tissues, but the results were often contradictory and always unsatisfactory. After many fruitless efforts with various culture mediums, Noguchi finally discovered that when strict anaerobiosis and a medium consisting of serum water to which is added sterile tissue from the rabbit's testicle or kidney are employed, the *Treponema pallidum* can be cultivated in a pure state.[3] Noguchi next cultivated anaerobically two strains of the isolated spirochetes, employing for that purpose ascitic fluid and ascitic-fluid-agar, both containing a piece of sterile placenta. By grinding in a mortar the agar columns containing innumerable spirochetes, and diluting the resulting paste with the inoculated fluid culture, an emulsion was prepared to which, after it had been heated for one hour to 60 C., 0.5 per cent. of phenol was added. This emulsion, which Noguchi named luetin, is a slightly viscid, opalescent, sterile fluid which under the dark-field microscope revealed from forty to 100 dead pallida per field. Noguchi also prepared for use as a control a sterile carbolized emulsion, exactly the same as the above with the exception that it was not inoculated with the pallidum. Both emulsions are to be kept in a refrigerator when not in use.

*Read in the Section on Medicine, New York Academy of Medicine, Dec. 19, 1911.

1. Von Pirquet, C. E.: Allergy, THE ARCHIVES INT. MED., 1911, vii, 288.

2. Schoenberg, M. J., and Burchill, E.: A Few Suggestive Experiments for a Cutaneous Reaction for the Diagnosis of Syphilis, New York Med. Jour., 1911, xciv, 784.

3. Noguchi, Hideyo: A Method for the Pure Cultivation of Pathogenic Treponema Pallidum, Jour. Exper. Med., 1911, xiv, 99.

Noguchi now performed inoculation experiments first in syphilitic rabbits and later in human beings. The method of preparation of the luetin, the specific cutaneous reaction obtained therewith in suitable cases and the simple technics employed are fully described in Noguchi's recent article.[4]

The only one who has thus far had a considerable practical experience with the luetin test, besides Dr. Noguchi, is Dr. Martin Cohen, who at the outset was supplied with the emulsions and who has performed the test during the past six months in over 200 cases; I wish to express my indebtedness to Dr. Cohen for the privilege of observing many of the tests and also for having performed it on a number of my patients.

Technic of Intradermatic Injections.—Employing a glass syringe with a fine sharp needle, the control emulsion is injected into the cleansed skin of the forearm or arm on one side and the luetin injected at a corresponding site on the opposite side. The needle is made to enter the skin just beneath the epidermis and one drop (about 0.1 c.c.) is injected so as to produce a pale swelling which usually disappears within twenty minutes.

Local Appearances.—At both sites, in normal individuals and in negative tests, besides the minute trauma due to the needle, there results an erythematous halo which seldom lasts longer than forty-eight hours and has usually receded within twenty-four hours. There is no induration and there remains only an ecchymotic area due to the trauma.

In positive reactions, on the other hand, the luetin can produce a variety of effects which can be classified as follows:

1. Erythema with induration: This mildest type of reaction appears in from twenty-four to twenty-eight hours, when it either develops into the next form or undergoes retrogression; when the latter occurs the induration persists for a variable period.

2. Papular Form: After twenty-four to forty-eight hours the redness and induration increase for three or four days till a papule from 5 to 20 mm. in diameter has been formed. This papule exhibits areolar telangiectasis and, in case the inflammation now subsides, persistent induration; but it frequently develops into the following form:

3. Pustular Form: On the fourth or fifth day the papule develops a central area of suppuration with subsequent rupture and extrusion of seropurulent fluid.

4. Torpid Form: In ten days or more, after the luetin test has apparently been negative, a small papule or pustule develops at the luetin site.

Occasionally a rectal temperature of 100 F., slight malaise and mild gastro-intestinal disturbance are observed during the development of the

4. Noguchi, Hideyo: A Cutaneous Reaction in Syphilis, Jour. Exper. Med., 1911, xiv, 557.

local inflammation, but as a rule there is no marked constitutional reaction even in markedly positive cases. Apparently the test is harmless, it having thus far (Dec. 15, 1911) been employed in over 650 cases without any ill-effects.

An interesting question is whether the modus operandi of the resulting local response in positive cases is the same with luetin as it is with Old Tuberculin, i. e., an anaphylactic phenomenon. There is some evidence in favor of this view; on giving successive luetin inoculations in the same individual there is sometimes a flare-up at the site of the original injection; again, the luetin test is generally negative in primary and secondary syphilis. On the other hand, the reaction might be due to a pathologically sensitive condition of the skin resulting from previous selective activity of the syphilitic poison; in other words, a condition of cutaneous hypersensitiveness which is not hypersusceptibility in the anaphylactic sense. Though Noguchi believes otherwise, he mentions, as a possible explanation of the reaction, this peculiar susceptibility of the skin of syphilitics to traumatic irritation, which has been spoken of by Neisser as *Umstimmung*. Noguchi and Cohen have observed independently that occasionally a positive luetin test in syphilis is accompanied by a reaction at the control site, but that the control reaction is always of lesser intensity and is not followed after recession of the inflammation by the characteristic induration which persists at the luetin site for a variable but considerable period.

Be this question as it may, the practical results from the two tests which are theoretically analogous are likely to be very different. Let us for a moment consider the negative side of the question and compare the results obtained with Old Tuberculin inoculated into the skin of non-tuberculous patients, and the results which Cohen has obtained with luetin injected intradermatically in non-syphilitic cases. It is well known that the von Pirquet test is of litle practical value in adults for the reason that so many adults have been previously sensitized by some tuberculous infection; from a recent exhaustive study of the tuberculin test at Johns Hopkins, Hamman and Wolman reported 57 per cent. of positive von Pirquet reactions in apparently non-tuberculous adults.[5] In Cohen's patients, who were clinically and serologically non-syphilitic and who were suffering from minor ailments or various infectious diseases other than syphilis, the luetin tests were regularly negative. Noguchi and Cohen have reported that in fifty normal individuals, forty-seven of the luetin tests were absolutely negative and three gave mild and atypical inflammatory responses easily distinguishable from positive reactions. Consequently, on the one hand, in non-tuberculous individuals, there were

5. Hamman, L. and Wolman, S.: The Cutaneous and Conjunctival Tuberculin Tests in the Diagnosis of Pulmonary Tuberculosis, The Archives Int. Med., 1909, iii, 307; 1910, vi, 690.

57 per cent. positive von Pirquet reactions; on the other hand, in non-syphilitic individuals, there were constantly negative luetin tests. Apparently, therefore, the test is of considerable negative value.

As to the positive value of the test, it has rarely been positive in primary syphilis, inconstantly in secondary syphilis, and seldom in parasyphilitic conditions. Fortunately the very stages of syphilis in which such a diagnostic aid is most needed reveal the most marked and constant reactions, namely, hereditary and tertiary syphilis. Noguchi reports more than 90 per cent. of positive reactions in latent and manifest tertiary syphilis and in congenital syphilis. Syphilis being a frequent causative factor in certain eye diseases, notably interstitial keratitis, Cohen[6] performed the test in sixty ophthalmological cases either suspected of being or known to be syphilitic, and compared the results with the clinical evidence and Wassermann reaction. He found that the test corresponded in 76⅔ per cent. of the cases either with the Wassermann and clinical evidence together or with one of these factors of comparison separately. One important observation which Cohen made in the course of these studies was that in a number of cases in which negative Wassermann reactions were presumably the result of recent treatment, the luetin test was positive. To what extent the test can be utilized to determine whether a syphilitic infection has been permanently suppressed is not definitely known as yet. That the Wassermann reaction is inadequate for this purpose is proved by the following experience:

A New York physician whose accidental extragenital infection occurred in 1905 was energetically treated with salicylate injections for four years. For two years more the Wassermann test, made at intervals of six months, was always negative; nevertheless a gumma of the tongue developed three months ago, the Wassermann becoming positive at this time. On intravenous administration of salvarsan the tumor promptly retrograded, and at the present time, after two months of mercurial treatment, the Wassermann reaction and luetin test are both negative.

In another case (W. A. W.) of manifest tertiary syphilis successfully treated with salvarsan and mercury, the Wassermann reaction and luetin test are both negative.

In a case (D. L. D.) of virulent syphilitic infection of two years' duration, in which there have been relapses despite prolonged administration of mercury and two injections of salvarsan, the Wassermann test (taken while the patient was under mercurial treatment) is still positive and the luetin test negative.

According to Martin Cohen, who has had similar results in several of his own patients, owing to the virulence of the infection anaphylaxis has not become established in the case last mentioned. Were the infection to respond to treatment the Wassermann should become negative and the luetin test positive; were the patient to be finally cured, both tests should be negative.

6. Cohen, Martin: Noguchi's Cutaneous Luetin Reaction and Its Application in Ophthalmology, Arch. Ophth., 1912, xli, 8.

In conclusion it may be said that if the harmlessness of the procedure and if the results thus far obtained are confirmed by other observers, the reaction is of considerable practical importance and likely to have far-reaching consequences in the future diagnosis of syphilis.

SUMMARY

1. The luetin test is a simple harmless procedure consisting essentially of the intradermatic injection of a carbolized emulsion containing dead *Spirochætæ pallidæ*.

2. The reaction is negative in normal and non-syphilitic individuals and in various diseases including tuberculosis, pneumonia, typhoid fever, malaria, carcinoma, eczema and psoriasis (Noguchi).

3. The test can already be accepted as of considerable negative value. As compared with the von Pirquet reaction, the latter gives more than 50 per cent. positive reactions in apparently non-tuberculous adults, whereas the luetin test is constantly negative in both adults and children who are clinically and serologically non-syphilitic.

4. The positive value of the test appears to be more limited. A positive reaction is rarely obtained in primary syphilis and inconstantly in secondary syphilis. Noguchi found the test unsatisfactory in para-syphilitic conditions. Whether the negative reactions usually obtained in patients practically cured of syphilis indicate lasting suppression of the disease remains to be determined.

In hereditary and tertiary syphilis, however, Noguchi obtained positive reactions in more than 90 per cent. of the cases.

According to Martin Cohen's studies, in eye affections supposedly syphilitic in etiology, the reaction corresponds with the clinical evidence or with the Wassermann reaction in 76⅔ per cent. of cases. In a number of Cohen's cases in which negative Wassermann reactions were presumably due to recent treatment, the luetin test was positive.

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